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(71) Applicant: Tanabe Seiyaku Co., Ltd.
No. 21 Dosho-machi 3-chome Higashi-ku
Osaka-shi Osaka-fu(JP)

(72) Inventor: Hayashi,Kimiaki
G-104, No. 27, Shin-Ashiya-Kami
Suita-shi, Osaka-fu(JP)

(72) Inventor: Kato, Jyoji
No. 25-16, Yoshii
Otokoyama Yawata-shi, Kyoto-fu(JP)

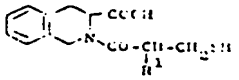
(72) Inventor: Uchida, Tomofumi
No. 10-22-509, Miigaoka 1-chome
Neyagawa-shi, Osaka-fu(JP)

(72) Inventor: Yoneda, Naoto
A-409, No. 34, Senrioka-Naka
Suita-shi, Osaka-fu(JP)

(74) Representative: Eitle, Werner, Dipl.Ing. et al,
Arabellastrasse 4 Sternhaus
D-8000 München 81(DE)

(54) **Tetrahydroisoquinoline compounds, process for preparing same and pharmaceutical compositions containing them.**

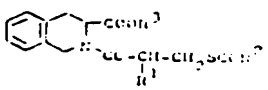
(57) A compound of the formula:

(I) 

wherein R^1 is hydrogen or methyl, is prepared by condensing a compound of the formula:

(II) $R^2CO\text{-}SCH_2CH(R^1)\text{-}COOH$

wherein R^2 is alkyl, aryl or aralkyl and R^1 is same as above, or a reactive derivative thereof with 1,2,3,4,-tetrahydroisoquinoline -3-carboxylic acid or an ester thereof to give a compound of the formula:

(IV) 

wherein R^3 is an ester residue and R^1 and R^2 are same as above, followed by hydrolysis or ammonolysis of said compound (IV).

The compound (I) is useful as a diagnostic or therapeutic agent for angiotensin-related hypertension.

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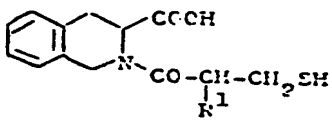
Novel tetrahydroisoquinoline compounds and process for preparing same

This invention relates to a novel tetrahydroisoquinoline compound and a process for preparing same. More particularly, it relates to a compound of the general formula:



(I)

wherein R^1 is hydrogen or methyl, or a pharmaceutically acceptable salt thereof.

It is known that the action of the enzyme renin on angiotensinogen, a pseudogloblin in blood plasma, produces angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II which is an active pressor substance and is causative of various forms of hypertension in mammalian species. It is also known that ACE decomposes or inactivates bradykinin, the vasodepressor substance in blood plasma, thereby serving to increase blood pressure. Thus, intensive studies have been made in recent years to investigate ACE-inhibitors because such inhibitors may prevent

the formation of the pressor substance angiotensin II or the decomposition of bradykinin and be used for the treatment of patients with high blood pressure. For example, M.A.Ondetti et al disclose that azetidine-2-carboxylic acid derivatives such as N-(3-mercapto-2-methylpropionyl)-L-proline intervene in the renin →angiotensin I→angiotensin II sequence by inhibiting angiotensin-converting enzyme and can be used in alleviating angiotensin-dependent hypertension (U.S.Patent No. 4,046,889). I. Mita et al also disclose that (4R)-3-[(2S)-3-mercapto-2-methyl-propionyl]-4-thiazolidinecarboxylic acid is an ACE-inhibitor (Chem. Pharm. Bull. 26(1978), 1333 - 1335).

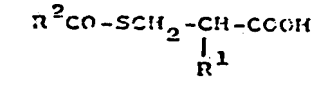
As a result of various investigations, we have now found that the novel tetrahydroisoquinoline compound (I) of the present invention shows potent inhibitory activity against angiotensin-converting enzyme (ACE) and is useful as a diagnostic or therapeutic agent for angiotensin-related hypertension. For example, when said inhibitory activity was estimated *in vitro* by the use of ACE isolated from pig's kidney, (3S)-2-[(2S)-3-mercapto-2-methyl-propionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid of the invention showed 50 % inhibition of the activity of the enzyme at a concentration of about 1.5×10^{-8} moles/liter. Moreover, the compound (I) of the present invention decreases aggregation of blood platelets and can be used to improve blood flow disturbances or other vascular diseases due to the formation of platelet aggregates (i.e., thrombus). Since the hypertensive disease is largely found in the aged subjects who show an increased tendency to capillary fragility or thrombosis, therefore, the compound (I) of the invention is useful to prevent, in addition to the treatment

of hypertension, the genesis of thrombosis and other occlusive vascular diseases of such subjects. Further, the toxicity of the compound (I) is considerably low. For example, when (3S)-2-[(2S)-3-mercapto-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline was administered orally to mice at a dose of 3 g/kg, no mouse died five days after said administration.

The compound (I) of the present invention can be used for pharmaceutical use either as the free acid or a salt thereof. Pharmaceutically acceptable salts of the compound (I) include, for example, inorganic salts such as sodium, potassium, calcium and magnesium salts, organic salts such as lysine, arginine and dicyclohexylamine salts, and the like. A daily dose of the compound (I) or a salt thereof may be about 30 mg to about 3 g, especially 50 mg to one g, per body of patients. Further, the compound (I) or a salt thereof may be used in the form of a pharmaceutical preparation containing the same compound in conjunction or admixture with a pharmaceutical excipient suitable for oral or parenteral administration. Suitable excipients include, for example, starch, lactose, glucose, potassium phosphate, corn starch, arabic gum, stearic acid and other known medicinal excipients. The pharmaceutical preparations may be in solid form such as tablets, pills or capsules; or in liquid form such as solutions, suspensions or emulsions. They may be sterilized and/or may further contain auxiliaries such as stabilizing, wetting or emulsifying agents. While the compound (I) of the present invention in which R^1 is methyl involves four optical isomers due to the two asymmetric carbon atoms, either one of said optical isomers or diastereoisomers thereof may be used for medicinal purposes. If

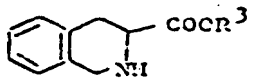
required, a mixture of said four isomers may be used.

According to the present invention, the compound (I) can be prepared by (i) condensing a propionic acid compound of the formula:



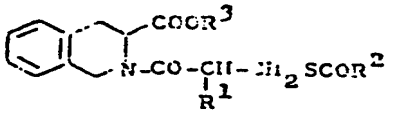
(II)

wherein R^2 is alkyl, aryl or aralkyl and R^1 is the same as defined above, or a reactive derivative thereof with a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid compound of the formula:



(III)

wherein R^3 is hydrogen or an ester residue, to give a compound of the formula:



(IV)

wherein R^1, R^2 and R^3 are the same as defined above, and then (ii) hydrolyzing the compound (IV). When R^3 is hydrogen, the compound (I) of the invention is also prepared by contacting the compound (IV) with ammonia.

The starting compound (III) of the invention may be obtained by a Pictet-Spengler reaction, i.e., by condensing phenylalanine and formaldehyde (Journal of The American Chemical Society 70, 180 (1948)), and if required, further esterifying the product in conventional manners. On the other hand, the starting compound (II) may be obtained by condensing an acrylic acid of the formula: $CH_2=C(R^1)-COOH$ (wherein R^1 is the same as defined above) with a thioic acid of the formula:

agent (e.g., dicyclohexylcarbodiimide) in a solvent (e.g., tetrahydrofuran, dioxane, dichloromethane, chloroform). Further, when R^3 is an ester residue, the compound (III) may be employed for the condensation reaction in the form of either free base or an acid addition salt thereof. Suitable examples of said acid addition salt are hydrochloride, hydrobromide, p-toeylate and the like.

The condensation reaction of the propionic acid compound (II) (free acid) with the compound (III) can be accomplished in the presence of a dehydrating agent in a solvent. Preferred examples of said dehydrating agent include dicyclohexylcarbodiimide, N, N'-carbonyldiimidazole and the like. Tetrahydrofuran, dioxane, dichloromethane and chloroform are suitable as the reaction solvent. It is preferred to carry out the reaction at a temperature between -10° and 50°C, especially 0° and 40°C.

The condensation reaction of the reactive derivative of the propionic acid compound (II) with the compound (III) can be effected in the presence of an acid acceptor in a solvent. For example, when the compound (III) is employed in the form of free acid (R^3 = H), said reaction is preferably carried out in the presence of an alkali carbonate (e.g., sodium carbonate, potassium carbonate) or an alkali hydroxide (sodium hydroxide, potassium hydroxide) in an aqueous solvent. Water or a mixture of water and acetone, tetrahydrofuran, dioxane or ether are suitable as the reaction solvent. On the other hand, when the compound (III) in the form of an ester (R^3 = ester residue) is employed, said reaction is preferably

convert said tert.-butyl ester into the corresponding free carboxylic acid, followed by hydrolysis or ammonolysis of the resultant product under the same conditions as described above. In the latter method, the treatment of the compound (IV) (R^3 = tert.-butyl) with trifluoroacetic acid or other acids is carried out at a temperature between -5° and 40°C. In every events, it is preferred that the hydrolysis and/or ammonolysis of the compound (IV) is carried out in an inert gas such as nitrogen or argon gas.

Since the above-mentioned reactions of the present invention are carried out without racemization, the compound (I) can be readily obtained in an optically active form by using the optically active enantiomer of the compound (III) as one of the starting materials of the invention. Further, when the compound (I) includes an asymmetric carbon atom on its side chain (i.e., when R^3 is methyl), the two diastereoisomers of the compound (I) may be preferably separated into each isomers by fractional recrystallization thereof.

Practical and presently-preferred embodiments of the present invention are illustratively shown in the following examples.

Experiments:

ACE-inhibitory effect of the compound (I) and the preventive effect thereof upon aggregation of blood platelets were investigated by the following methods and meterials.

Methods:

(A) ACE-inhibitory activity in vitro:

50 µl of a solution containing 0.01 mole/liter of hippuryl-histidyl-leucine (substrate) and 0 - 100 µl of a test compound solution were added to 300 µl of a 0.2M tris-hydrochloric acid buffer solution containing 0.2 mole/liter of sodium chloride. The total volume of said mixture was adjusted to 450 µl with water. Then, 50 µl of angiotensin-converting enzyme (ACE) isolated from pig's renal cortex were added to the mixture, and the mixture was allowed to stand at 37°C for 20 minutes. The amount of histidyl-leucine produced from the substrate by the action of ACE was assayed microbiologically by the use of Leuconostoc mesenteroides P-60, and the ACE-inhibitory activity of the test compound was estimated therefrom.

(B) ACE-inhibitory activity in vivo:

Normotensive rats weighing 300 - 400 g were anesthetized with urethane(1.5 g/kg, s.c.), and angiotensin I (300 ng/kg) was injected into the femoral vein of the rats. The pressor response to angiotensin I was measured with a pressure transducer connected to the carotid artery. Then, a test compound was injected intravenously thereto at a dose of 0.1 mg/kg, and angiotensin I (300 ng/kg) was further injected intravenously at intervals. The ACE-inhibitory

activity of the test compound was estimated from the pressor responses to angiotensin I which were obtained before and after intravenous injection of the test compound.

(C) Hypotensive activity in SHR:

A test compound (dose: 50 mg/kg) suspended in an aqueous carboxymethylcellulose solution was administered orally to spotaneously hypertensive rats (SHR) fasted for a day. The systolic blood pressure of the rats was measured by the tail plethysmographic technique (The Journal of Laboratory and Clinic Medicine 78(1971), page 957). The hypotensive activity of the test compound was estimated from the decreased level of blood pressure.

(D) Platelet aggregation-inhibiting activity:

Nine volumes of blood collected from the accessary cephalic vein of male beagle dogs (body weight: 10 - 14 kg) were mixed with one volume of an aqueous 3.8 % trisodium citrate solution, and the mixture was centrifuged at 250 x g for 5 minutes to give platelet-rich plasma (PRP) as the upper layer. The bottom layer was further centrifuged at 1000 x g for 15 minutes to give platelet-poor plasma (PPP) as the supernatant solution. PRP was diluted with PPP so that the blood platelet count was about 4 x 10^5 cells/mm^2. Then, ADP was added to the diluted PRP, and the degree of ADP-induced platelet aggregation was examined by Born's method (Nature 194(1962), page 927). The solution of a test compound (100 µg/ml) was added to the diluted PRP 2 minutes before addition of ADP, and the platelet aggregation-inhibiting activity thereof was estimated in terms of the percentage inhibition of the second

wave of ADP-induced platelet aggregation.

Results:

The results are shown in the following tables.

Table 1

Test compounds	ACE-inhibitory activity in vitro I_{50}(mol/liter)*	Platelet aggregation -inhibiting activity**
(3S)-2-[(2S)-3-mercapto-2-methyl-propionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	1.5×10^{-8}	86 %
2-(3-mercaptopropionyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic salt	8.1×10^{-8}	68 %

Note: * : I_{50} = a dose required to induce 50 % inhibition of the ACE activity

**: percentage inhibition of the second wave of ADP-induced platelet aggregation

Table 2

Test compounds	ACE-inhibitory activity in vivo*	Hypotensive activity in SHR	
		Decrease in blood pressure	Duration of action
(3S)-2-[(2S)-3-mercapto-2-methyl-propionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	90 %	ca. 20 %	>6 hours

Note: * : percentage inhibition of ACE activity in vivo

Example 1

(1) 5.69 g of methyl (3S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride are suspended in 50 ml of chloroform, and 5.6 g of triethylamine are added thereto under ice-cooling and stirring. 3-benzoylthio-2-methylpropionyl chloride (which is prepared by heating a mixture of 5.6 g of 3-benzoylthio-2-methyl-propionic acid and 6 ml of thionyl chloride at 60°C for 2 hours, followed by distillation thereof to remove the excess of thionyl chloride) is dissolved in 10 ml of tetrahydrofuran, and said tetrahydrofuran solution is added dropwise to the suspension obtained above. After the mixture is stirred at room temperature overnight, the chloroform layer is collected therefrom and washed with water, an aqueous sodium bicarbonate solution, diluted hydrochloric acid and water, successively. The chloroform solution is dried and then distilled to remove solvent. The residue thus obtained is purified by silica gel column chromatography (Solvent, toluene-ethyl acetate (4 : 1)). 8.0 g of methyl (3S)-2-(3-benzoylthio-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate are obtained as colorless oil. Yield: 80.5 %

$IR\nu_{max.}^{liq.}$ (cm^{-1}): 1740, 1660, 1640

(2) 8.0 g of methyl (3S)-2-(3-benzoylthio-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate are dissolved in 30 ml of methanol, and 60 ml of an aqueous 1N-sodium hydroxide solution are added thereto. The mixture is stirred at room temperature for 3 hours in nitrogen gas atmosphere. The reaction mixture is made weak-acidic with hydrochloric acid

and then distilled under reduced pressure to remove methanol. The residue is extracted with ethyl acetate. The extract is washed with water, dried and distilled to remove solvent. The oily residue thus obtained is introduced into a silica gel column, and washed with ethyl acetate-chloroform (1 : 1) to remove benzoic acid. Then, the column is eluted with ethyl acetate-acetone (3 : 2). The eluate is condensed under reduced pressure, whereby 3.9 g of (3S)-2-(3-mercapto-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid are obtained as colorless viscours oil. Yield: 69.8 %

(3) 3.9 g of this product and 2.5 g of dicyclohexylamine are dissolved in 30 ml of ether. n-Hexane is added to the solution, and the mixture is allowed to stand at room temperature. Crystalline precipitates are collected by filtration. Then, the precipitates obtained are recrystallized from a mixture of ethyl acetate and ether and further recrystallized from ethanol. 1.6 g of (3S)-2-[(2S)-3-mercapto-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid·dicyclohexylamine salt are obtained as colorless crystals. M.p. 191 - 192°C(decomp.) (softened at about 172°C)

IR $\nu_{max.}^{KBr}$ (cm^{-1}): 3500, 1630, 1560

Mass (free acid) m/e: 279 (M^+)

$[\alpha]_D^{26}$ -21.0°(C=1, methanol)

Free acid (recrystallized from ethyl acetate-n-hexane):

M.p. 134 - 135°C

$[\alpha]_D^{26}$ -22.0°(C=1, methanol)

Example 2

(1) 2.3 g of 1,2,3,4-tetrahydroisoquinoline-3-

carboxylic acid are dissolved in 100 ml of water containing 2.6 g of potassium carbonate. 3-benzoylthio-propionyl chloride (prepared from 2.1 g of 3-benzoylthio-propionic acid and 4 ml of thionyl chloride) is dissolved in 15 ml of ether, and said ether solution is added dropwise to the aqueous solution obtained above. After the mixture is stirred for 3 hours under cooling, the aqueous layer is collected therefrom and is made acidic with hydrochloric acid. Said aqueous solution is extracted with ethyl acetate. The extract is washed with water, dried and then distilled to remove solvent. The residue thus obtained and 1.9 g of dicyclohexylamine are dissolved in ether. n-Hexane is added to the solution, and the mixture is allowed to stand at room temperature. Crystalline precipitates are collected by filtration. 1.5 g of 2-(3-benzoylthio-propionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.dicyclohexylamine salt are thereby obtained. M.p. 202 - 203°C(decomp.) (This product begins to gradually decompose at 188°C)

IR $\nu_{max.}^{nujol}$ (cm^{-1}): 1665, 1640, 1560

Mass (free acid) m/e: 369 (M^+)

(2) 1.4 g of 2-(3-benzoylthio-propionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid dicyclohexylamine salt are dissolved in 20 ml of methanol, and 20 ml of 5 % aqueous ammonia are added thereto. The mixture is stirred at room temperature overnight in nitrogen gas atmosphere. The reaction mixture is condensed to dryness under reduced pressure, and the residue is washed with ether. 0.35 g of 2-(3-mercaptopropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.dicyclohexylamine salt is thereby obtained. Yield: 74.7 % M.p. 193 - 194°C(decomp.)

(This product begins to gradually decompose at 176°C).

$IR\nu_{max.}^{nujol}(cm^{-1})$: 1635, 1560

Mass (free acid) m/e: 265 (M^+)

Example 3

(1) 3.73 g of tert.-butyl (3S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, 3.58 g of 3-benzoylthio-2-methylpropionic acid and 2.16 g of 1-hydroxybenzotriazole are dissolved in 60 ml of tetrahydrofuran, and a solution of 3.3 g of dicyclohexylcarbodiimide in 10 ml of tetrahydrofuran is added dropwise thereto at -15°C. After said dropwise addition, the mixture is stirred at a temperature below -10°C for 3 hours and then at room temperature overnight. Insoluble materials are removed by filtration. The filtrate is distilled under reduced pressure to remove solvent. Water is added to the residue obtained, and the aqueous mixture is extracted with ethyl acetate. The extract is washed with an aqueous 3 % citric acid solution, water, an aqueous sodium bicarbonate solution and water, sucessively. Then, the extract is dried and distilled to remove solvent. The residue thus obtained is purified by silica gel column chromatography. 5.10 g of tert.-butyl (3S)-2-(3-benzoylthio-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate are thereby obtained as colorless oil.

Yield: 73.7 %

Mass m/e: 439 (M^+)

(2) A solution of 5.13 g of tert.-butyl (3S)-2-(3-benzoylthio-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate in 20 ml of trifluoroacetic acid is allowed to stand at room temperature for one hour. The reaction solution

is distilled under reduced pressure to remove solvent. Ethyl acetate and an aqueous sodium bicarbonate solution is added to the residue. After shaking the mixture, the aqueous layer is collected therefrom and is made acidic with diluted hydrochloric acid. Then, the aqueous solution is extracted with ethyl acetate. The extract is washed with water, dried and then distilled to remove solvent. 4.4 g of (3S)-2-(3-benzoylthio-2-methylpropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid are thereby obtained as pale yellow oil. Yield: 97.2 %

4.4 g of this product are dissolved in about 20 ml of ether, and 2.1 g of dicyclohexylamine are added thereto. Said mixture is distilled to remove ether. After the residue is washed with n-hexane, ether is added to said residue. Crystalline precipitates are collected by filtration, whereby 2.15 g of (3S)-2-[(2S)-3-benzoylthio-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.dicyclohexylamine salt are obtained as colorless crystals. Yield: 32.3 %

M.p. 164 - 166°C(recrystallized from ethyl acetate-ether)

$IR\nu_{max.}^{KBr}(cm^{-1})$: 1665, 1630

Mass m/e(free acid): 383 (M^+)

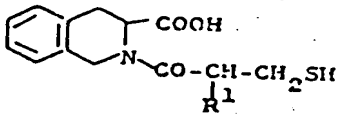
NMR($CDCl_3$)δ(free acid): 1.1 - 1.5 (3H, $C\underline{H}_3$), 2.8 - 3.5 (5H, $C\underline{H}_2$ at 4th-position of isoquinoline skeleton, $-S-C\underline{H}_2-C\underline{H}-$), 4.5 - 5.0(2H, $C\underline{H}_2$ at the 1st-position of isoquinoline skeleton), 5.2 - 5.5(1H, hydrogen atom at the 3rd-position of isoquinoline skeleton), 7.10(4H, hydrogen atoms at 5th, 6th, 7th and 8th-positions of isoquinoline skeleton), 7.25 - 8.10(5H, $-CO-C_6\underline{H}_5$)

(2) 1.20 g of (2S)-2-[(2S)-3-benzoylthio-2-methylpropionyl]-

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid dicyclohexylamine salt are suspended in a mixture of 15 ml of 10 % aqueous ammonia and 5 ml of methanol. The mixture is stirred at room temperature for 3.5 hours in nitrogen gas atmosphere. The reaction mixture is condensed to dryness under reduced pressure, and a mixture of ether and n-hexane is added thereto. Crystalline precipitates are collected by filtration, washed with ether and recrystallized from ethanol. 0.85 g of (3S)-2-[(2S)-3-mercapto-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid·dicyclohexylamine salt is thereby obtained as colorless crystals. Yield: 82.7 %. M.p. 191° - 192°C(decomp.)(This product begins to gradually decompose at about 172°C). All the physico-chemical properties of this product are identical with those of the sample obtained in Example 1-(3).

WHAT WE CLAIM IS:

1. A compound of the formula:



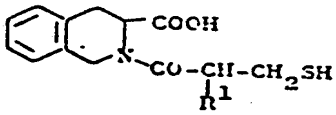
(I)

wherein R^1 is hydrogen or methyl, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, in which R^1 is methyl.

3. The compound of Claim 1 which is (3S)-2-[(2S)-3-mercapto-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline or a pharmaceutically acceptable salt thereof.

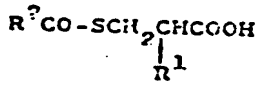
4. A process for preparing a compound of the formula:



(I)

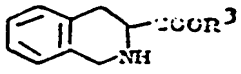
wherein R^1 is hydrogen or methyl, or a pharmaceutically acceptable salt thereof, which comprises the steps of:

(i) condensing a propionic acid compound of the formula:



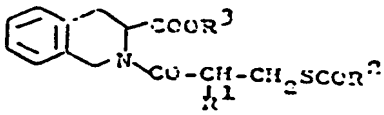
(II)

wherein R^2 is alkyl, aryl or aralkyl and R^1 is the same as defined above, or a reactive derivative thereof with a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid compound of the formula:



(III)

wherein R^3 is hydrogen or an ester residue, to give a compound of the formula:



(IV)

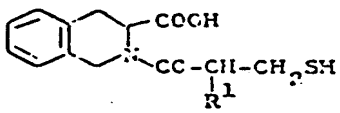
wherein R^1, R^2 and R^3 are the same as defined above,

(ii) hydrolysing the compound (IV) or contacting it with ammonia, and

(iii) if required, further converting the product into a pharmaceutically acceptable salt thereof.

5. The process according to Claim 4, wherein the condensation reaction of the compounds (II) and (III) is carried out at -10° to 50°C in the presence of a dehydrating agent in a solvent; the condensation reaction of the compound (III) with the reactive derivative of the compound (II) is carried out at -10° to 50°C in the presence or absence of an acid acceptor in a solvent; the hydrolysis of the compound (IV) is carried out at -10° to 50°C; or the compound (IV) is contacted with ammonia at -5° to 50°C in a solvent.

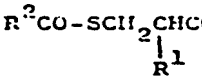
6. A process for preparing a compound of the formula:



(I)

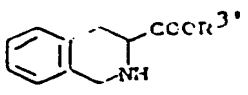
wherein R^1 is hydrogen or methyl, or a pharmaceutically acceptable salt thereof, which comprises the steps of:

(i) condensing a propionic acid compound of the formula:



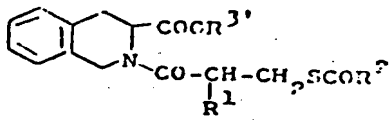
(II)

wherein R^2 is alkyl, aryl or aralkyl and R^1 is the same as defined above, or a reactive derivative thereof with a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid compound of the formula:



(III')

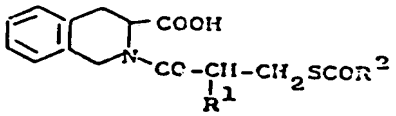
wherein $R^{3'}$ is tert.-butyl, to give a compound of the formula:



(IV')

wherein R^1, R^2 and $R^{3'}$ are the same as defined above,

(ii) treating the compound (IV') with an acid to give a compound of the formula:



(V)

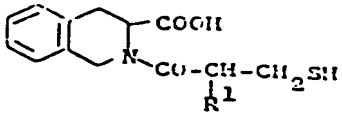
wherein R^1 and R^2 are the same as defined above,

(iii) further hydrolyzing the compound (V) or contacting it with ammonia, and

(iv) if required, converting the product into a pharmaceutically acceptable salt thereof.

7. The process according to Claim 6, wherein the condensation reaction of the compounds (II) and (III) is carried out at -10° to 50°C in the presence of a dehydrating agent in a solvent; the condensation reaction of the compound (III) with the reactive derivative of the compound (II) is carried out at -10° to 60°C in the presence of an acid acceptor in a solvent; the treatment of the compound (IV') with the acid is carried out at -5° to 40°C; further hydrolysis of the compound (V) is carried out at -10° to 60°C; or the compound (V) is contacted with ammonia at -5° to 50°C in a solvent.

8. A pharmaceutical composition which comprises a compound of the formula:



wherein R^1 is hydrogen or methyl, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

European Patent Office

EUROPEAN SEARCH REPORT

0012845
Application number

EP 79 104 613 3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
P	EP - A1 - 0 001 978 (YOSHITOMI PHARMACEUTICAL INDUSTRIES) * claim 2 *	4,6
P	DE - A1 - 2 828 578 (YOSHITOMI PHARMACEUTICAL INDUSTRIES) * claim 29 *	4,6
D,A	US - A- 4 046 889 (M.A. ONDETTI et al.)	

CLASSIFICATION OF THE APPLICATION (Int. Cl.)

C 07 D 217/26
A 61 K 31/47

TECHNICAL FIELDS SEARCHED (Int. Cl.)

A 61 K 31/47
C 07 D 217/26

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate documen.
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document